The Role of Spatial Structure in Bacteriophage Evolution

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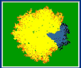
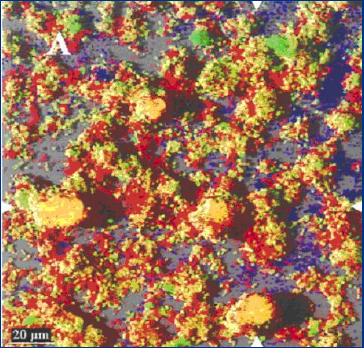


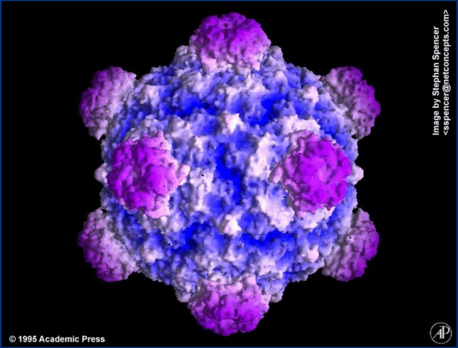


Spatial biofilm structure; *P. putida* (red), *Acinetobacter* (purple), with transconjugants (green and yellow) [Christensen, et al., *Appl. Environ. Microbiol.* (1998)]

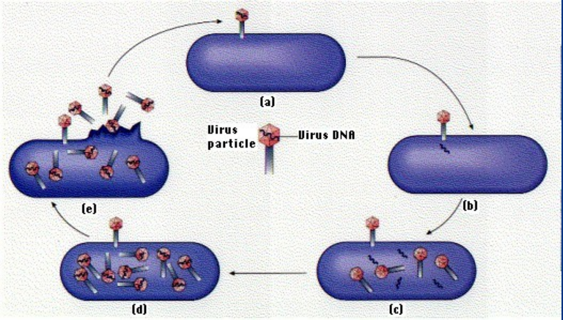
Microbial Experimental Evolution & Mathematical Modeling

- Most microbial communities grow in spatially structured environments (biofilm, soils, surfaces)
- Evolutionary and ecological dynamics often on similar time scales (experimental evolution possible)
- How does spatial structure affect these dynamics?
- Phage–Bacteria system
- Interacting Particle System model (randomness & spatial structure at individual cell level)

Phage ϕX174



Phage infection



Outline

- General host-pathogen system: fate of mutant pathogens in a radially expanding epidemic
  - the nuts and bolts of invasion
- Phage–Bacteria interactions
  - phage competition on plates (theory and experiment)
  - ecology/evolution

I. Fate of Mutant in Host-Pathogen System

states: Susceptible, Infective, Removed (dead)

Mass action ODE (well mixed):

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI + \cdots \\ \frac{dI}{dt} &= \beta SI - \delta I + \cdots\end{aligned}$$

Invasion by second pathogen (evolution of virulence):

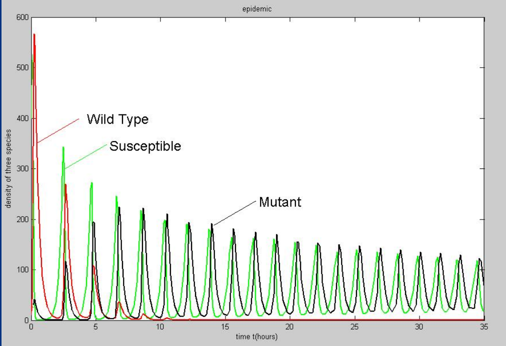
- $\beta_i =$ infection rate for I_i (host infected with virus i)
- $\delta_i =$ death rate (virulence) for I_i

Who wins?

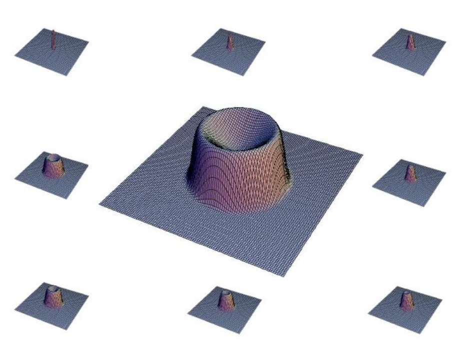
- Success determined by basic reproductive ratio:

$$R_0 = \frac{\beta S}{\delta}$$

- In well-mixed (liquid) culture, $\frac{\beta_2}{\delta_2} > \frac{\beta_1}{\delta_1}$ implies I_2 wins (independent of initial densities)
- Both pathogens encounter the same density of susceptible hosts

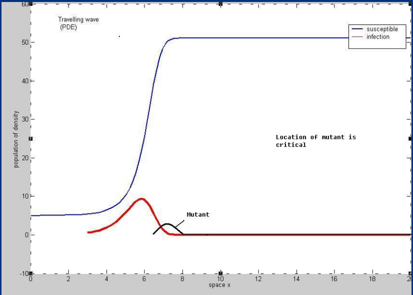

epidemic
600
500
400
300
200
100
0
density of three species
Wild Type
Susceptible
Mutant
0
5
10
15
20
25
30
35
time t(hours)

Partial Differential Equation



Wave Speed $c = 2\sqrt{D(\beta S - \delta)}$

Mutant pathogen at wave front



Fate of mutant determined by relative wave speeds and infectivities; not sensitive to ratio (except for invasion time).

- $c_2 > c_1$ and $\beta_2 > \beta_1$ $\Rightarrow$ mutant can invade from any position
- $c_2 > c_1$ and $\beta_2 < \beta_1$ $\Rightarrow$ mutant can invade from positions far enough toward front
- $c_2 < c_1$ $\Rightarrow$ mutant can never invade

IPS Simulations: single mutant pathogen

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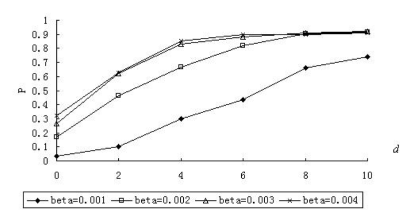
Simulation Data: single mutant

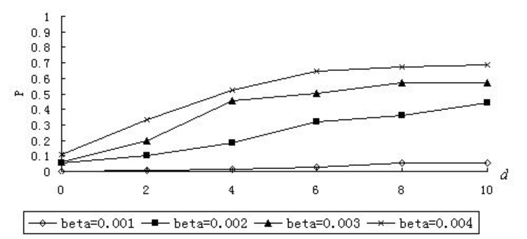
Invasion probability as function of mutant position (d = number of sites in advance of wavefront)



$\beta_1 = 0.002,\ \delta_1 = 0.0005\ \ (\beta_1/\delta_1 = 4)$

$\beta_2/\delta_2 = 10$; for large (fixed) ratio, infection rate matters

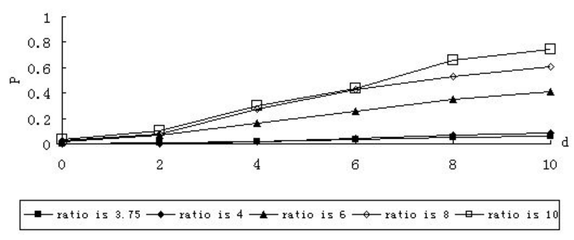
different ratio



$\beta_1 = 0.002,\ \delta_1 = 0.0005$ (ratio =4 always)

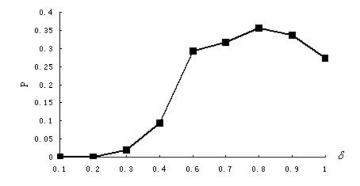
$\beta_2/\delta_2 = 3.75$ (smaller than wild type); once $\beta_2 > \beta_1$, easy to invade. But max is not as high as for large ratio.

smaller infectivity



Fixed $\beta_2 = 0.001$ (smaller); very hard to invade unless mutant starts far ahead of wild-type wave; large ratio then helps.

Trade-off



$\beta_i = \frac{c\delta_i}{1+\delta_i} \quad (c = 8, \beta_1 = 2.67, \delta_1 = .5)$

As δ_2 increases from 0.1 to 1, β_2 increases from .73 to 4, and ratio decreases from 7.27 to 4.

Max success prob at intermediate level of virulence (and transmissibility). Ratio and inf. rate both important.

IPS Simulations: spontaneous mutant pathogens

With small probability, individual pathogens mutate

Only mutants near edge have a chance to become established

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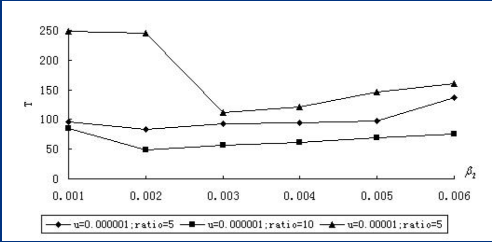
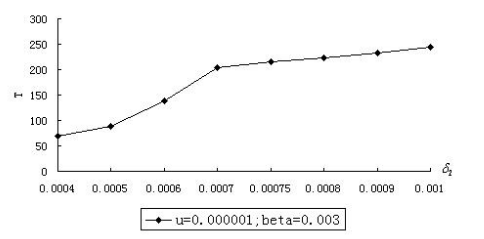
Time to first invasion



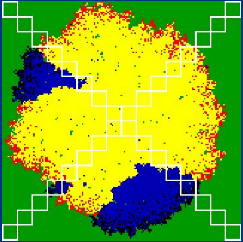
Time to first invasion

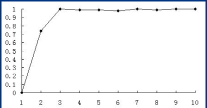


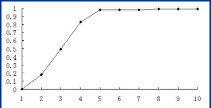
fix β_2 and change ratio

As δ_2 increases, ratio decreases; harder to invade. (Ratio important for successful invasion)

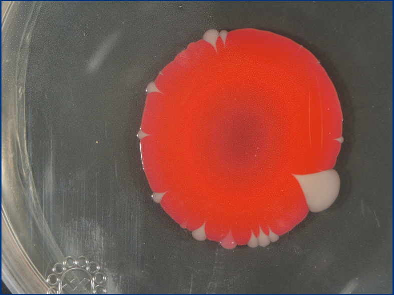
Simulation of Yin's Phage Experiment







Plasmid segregation and clonal wedges



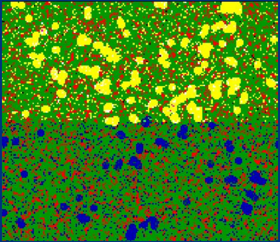
Segregation w/ different bacterial species

II. Phage competition and evolution on plates

Experimental System:

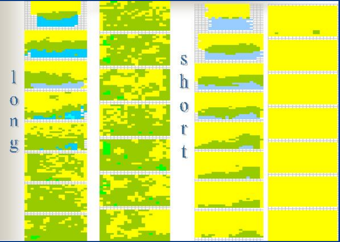
- ϕX and α3 . . . competing lytic phages
- α3 dominates in liquid setting
- ϕX dominates in spatial setting
- burst size vs. latent period
- effect of different passage times
- after a "passage" (5h or 18h), host cells are killed and some of phage are transferred using a "bed of nails" to fresh hosts (host cells must be actively dividing for virus to spread)

IPS simulations



yellow = ϕX, blue = α3, green = nutrient, red = host cells

Plate Experiments

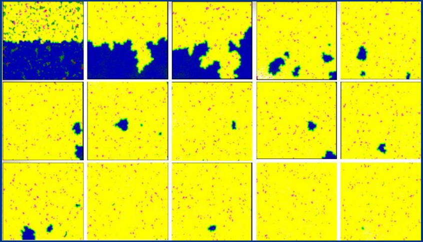


yellow = ϕX, blue = α3, green = both, light green = ϕX + resistant cell

5 h passages $\Rightarrow$ α3 dies out;

18 h passages $\Rightarrow$ Coexistence (resistant cells percolate).

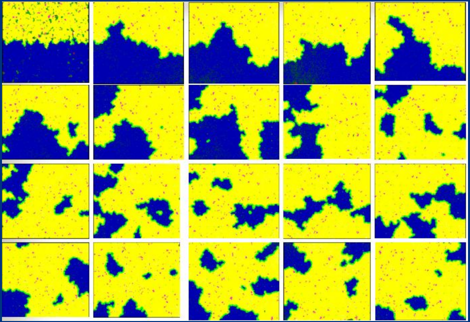
Short-passage simulations



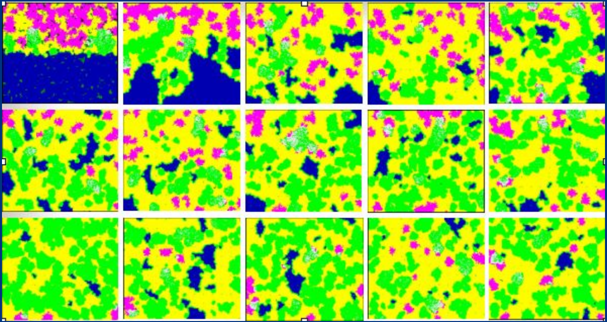
yellow = ϕX, blue = α3, green = both

Each picture shows configuration of phage at end of a "short" passage. Then transfer a sample and do another passage...

short passage; larger $\alpha 3$ burst size

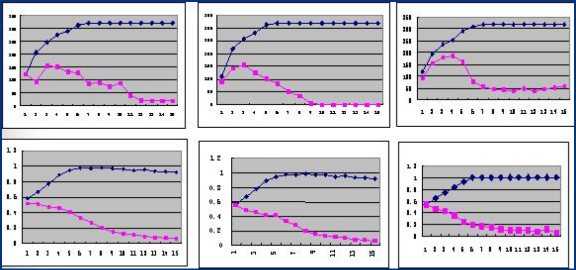


Long-passage simulations



Pink = ϕX-resistant cells + ϕX

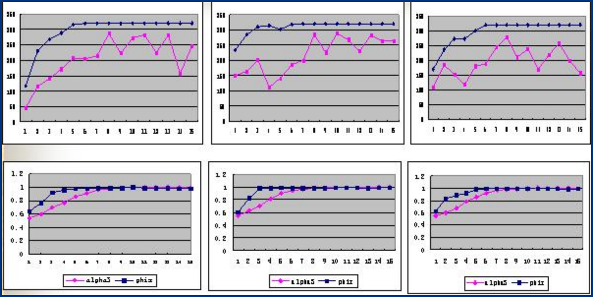
5-hour passages



3 runs (Top: experiments; Bottom: simulations)

$\alpha 3$ dies out (blue: ϕX pink: $\alpha 3$)

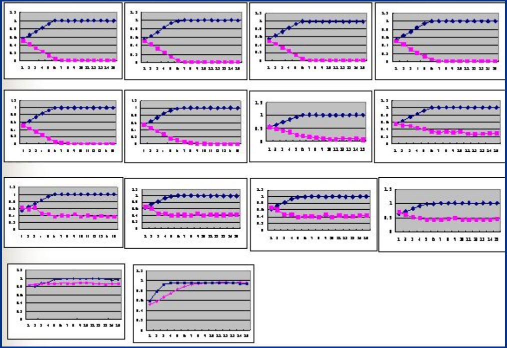
18-hour passages



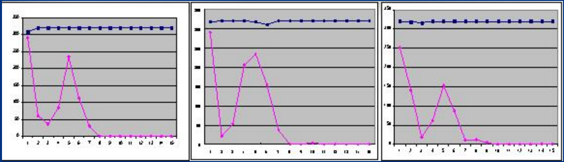
3 runs (Top: experiments; Bottom: simulations)

Coexistence (Oscillations in expt due to evolution of $\alpha 3$)

Effect of passage time (simulations)



Mixed plates–short passage time



Scrape-Mix-Plate. Oscillations due to evolution of $\alpha 3$.

Mixed plates–long passage times